Medical therapy to attenuate fetal anaemia in severe maternal red cell alloimmunisation

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DOI:
10.1111/bjh.17041

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Castleman, J, Moise JR, K & Kilby, M 2020, 'Medical therapy to attenuate fetal anaemia in severe maternal red cell alloimmunisation', *British Journal of Haematology*. https://doi.org/10.1111/bjh.17041

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References: 1. Esperoct® Summary of Product Characteristics. **2.** Adynovi® Summary of Product Characteristics. **3.** Elocta® Summary of Product Characteristics. **4.** Giangrande P et al. Thromb Haemost 2017; 117:252–261. **5.** Tiede A et al. J Thromb Haemost 2013; 11:670–678. **6.** Advate® Summary of Product Characteristics. **7.** NovoEight® Summary of Product Characteristics. **8.** Nuwiq® Summary of Product Characteristics. **9.** Refacto AF® Summary of Product Characteristics.

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Date of preparation: September 2020 UK20ESP00080

bjh review

Medical therapy to attenuate fetal anaemia in severe maternal red cell alloimmunisation

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Summary

Haemolytic disease of the fetus and newborn (HDFN) remains an important cause of fetal mortality with potential neonatal and longer-term morbidity. HDFN is caused by maternal red cell alloimmunisation, with IgG antibodies crossing the placenta to destroy fetal erythroid cells expressing the involved antigen. Intrauterine fetal blood transfusion is the therapy of choice for severe fetal anaemia. Despite a strong evidence base and technical advances, invasive fetal therapy carries risk of miscarriage and preterm birth. Procedure-related risks are increased when invasive, *in utero* transfusion is instituted prior to 22 weeks to treat severe early-onset fetal anaemia. This review focuses upon this cohort of HDFN and discusses intravenous immunoglobin (IVIg) and novel monoclonal antibody (M281, nipocalimab) treatments which, if started at the end of the first trimester, may attenuate the transplacental passage and fetal effects of IgG antibodies. Such therapy has the ability to improve fetal survival in this severe presentation of HDFN when early *in utero* transfusion may be required and may have wider implications for the perinatal management in general.

Keywords: anti-D, clinical trials, fetal medicine, fetal blood, immune haemolytic anaemia.

Fetal anaemia has heterogeneous aetiologies and early pregnancy screening, recognition of risk and timely *in utero* treatment is vital to avoid fetal death and adverse neonatal consequences.[1]

Haemolytic disease of the fetus and newborn (HDFN) is a pathologic disease process that if untreated and ameliorated, may cause increased perinatal mortality and morbidity.[2] It is commonly caused by maternal red blood cell (RBC) alloimmunisation, with IgG-class antibodies crossing the placenta to destroy fetal erythroid cells expressing the involved antigen. The most 'potent' antigens are D, Kell and c.[3,4] RBC alloantibodies are found in between 2% and 7% of the population[4,5] and over 50 different antigens may be responsible for HDFN.[6] HDFN affects 1/300–1/600 live births, as up to 1 in 80 pregnant women have clinically relevant RBC alloantibodies.[6–9]

Approximately 15% of white European women and about 5% of women of African and Indian ancestral origin are Rh-negative and do not express the D antigen on their RBCs.[10] Incompatibility with the 'D' antigen of the rhesus (Rh) group of RBC antigens is the main cause of HDFN and despite both prenatal and postnatal anti-D prophylaxis, approximately 1 in 1000 women still develop D alloimmunisation.[8] Other antigens, including 'c' and 'E' also cause alloimmunisation and severe HDFN due to the lack of available prophylaxis.[6] The 'K' and 'k' antigens of the Kell group are a less common cause of HDFN but the fetal anaemia associated with anti-Kell antibodies is unpredictable in onset because antibodies cause both RBC destruction and suppression of fetal erythropoiesis.[11,12]

International clinical guidance exists for management of alloimmunised pregnancies underpinned by a strong scientific evidence base.[13–17] In the United Kingdom, routine antenatal maternity care ascertains the maternal ABO and D blood group and screens alloantibody status in the first trimester and again at 28 weeks of gestation. Women with a previous pregnancy affected by HDFN or a critical level of high-risk alloantibody, should be referred early in pregnancy to a Fetal Medicine specialist for pregnancy assessment. Fetal genotype can be determined for antigens D, E, c and K utilising cell-free fetal DNA (cffDNA) analysis with a very high degree of sensitivity and specificity.[2,18,19] Alloantibody levels are usually measured four-weekly up to 28 weeks of gestation and fortnightly thereafter, so long as they remain stable. A rapid rise in levels (doubling in a 14-day period) or an increase above antigen-specific thresholds will alert clinicians to a high chance of HDFN. The management of women with red cell antibodies during

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doi: 10.1111/bjh.17041

pregnancy is outside the remit of this review but has been extensively reviewed.[15]

Pathophysiology

The fetal/neonatal Fc receptor (FcRn), a heterodimer, was first identified in the neonatal rodent intestine transporting IgG in breast milk.[20] FcRn is now recognised as an important transmembrane protein involved in IgG and albumin homeostasis and is present at the maternal–fetal interface (Fig 1).[21] FcRn in vascular endothelial cells plays a major role in immunoglobulin homeostasis by participating in the recycling of the circulating serum IgG pool. Expressed by the placental syncytiotrophoblast, FcRn transports maternal IgG subtypes across the placenta, by transcytosis, into the fetal circulation.[21] This transplacental transference is dependent upon: (i) the maternal level of total IgG and specific antibodies; (ii) gestational age of the pregnancy; (iii) placental 'integrity'; (iv) IgG characteristics including the subclass and degree and type of glycosylation;[22] and (v) the nature of the antigen (being more intense for thymus-dependent ones). It is also possible that pregnancy-related pathology itself may affect this process.[23] In health, this mechanism is protective, conferring passive immunity to the fetus and protecting IgG from degradation. In human disease, this mechanism is potentially harmful, such as in HDFN when alloantibodies enter the fetal circulation to target RBCs for destruction. Passage of the IgG1 subclass is most efficient and most readily causes HDFN.[24] The IgG3 subclass anti-RBC antibodies may also be pathogenic.[25]

Identification of the anaemic fetus

Direct fetal blood sampling is the gold standard for the diagnosis of fetal anaemia, but carries a procedure-related loss rate of up to 2%.[26–28] Doppler colour flow ultrasound to measure the fetal middle cerebral artery peak systolic velocity (MCA-PSV) is commonly utilised as a non-invasive screening test with an acceptable sensitivity and specificity for detecting (and excluding) fetal anaemia[29–32] and has led to the near disappearance of fetal hydrops at presentation.[33] This has replaced the assessment of OD450 in amniotic fluid but care should be practiced in using this screening test in timing serial intrauterine transfusions.[34] Fetal hydrops is an abnormal collection of fluid visualised by ultrasound in two or more body compartments (usually pericardial or pleural effusions, ascites or skin oedema).[35] It may be a characteristic ultrasound sign of severe fetal anaemia, usually associated with a haemoglobin deficit of greater than 70 g/l,[36] high output cardiac failure and associated with reduced tissue perfusion and oxygenation.[37] However, in the second trimester the fetus may be severely anaemic and the association with fetal hydrops is variable.

Invasive fetal therapy with intrauterine blood transfusion

Since the pioneering work of Liley in New Zealand in the 1960s, when he transfused donor red blood cells into the peritoneal cavity of an anaemic fetus in a pregnant women with Rh(D) alloimmunisation, this fetal therapy has been utilised.[38] This was followed by hysterotomy direct access to the fetal circulation[39] and then Rodeck gaining direct access to the fetal circulation by endoscopy and transfusing a baby *in utero*.[40] Today, the ultrasound-guided percutaneous needle access to the umbilical cord[41] or the intrahepatic vein[42–44] is relatively routine. This fetal therapy is perhaps arguably the most successful fetal treatment administered and is associated with low risks of miscarriage, amniorrhexis and technical failure.[45] However, it may be associated with additional induction of maternal alloantibodies.[46] The largest reported retrospective study of 1 678 intrauterine transfusions (IUTs) in 589 fetuses over three decades in The Netherlands showed that routine use of fetal paralysis, the avoidance of transamniotic cord and umbilical arterial puncture, and a preference for the intrahepatic route for IUT, reduced the procedure-

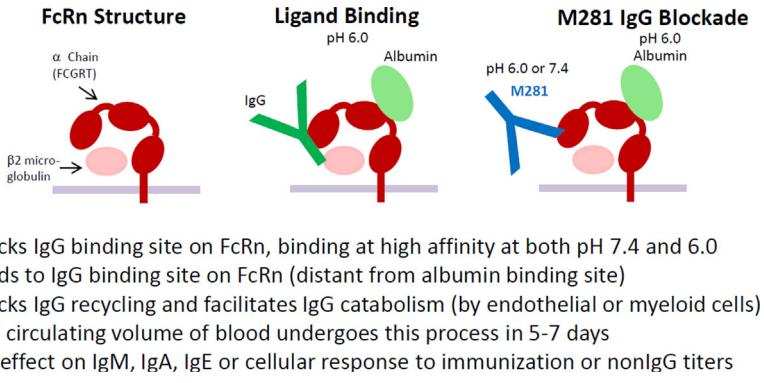
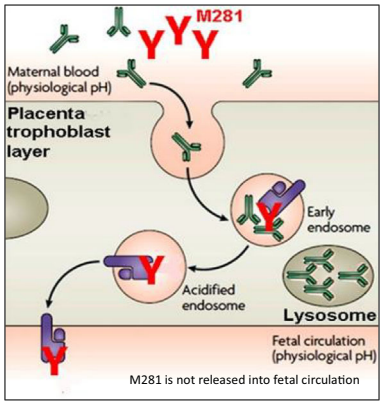


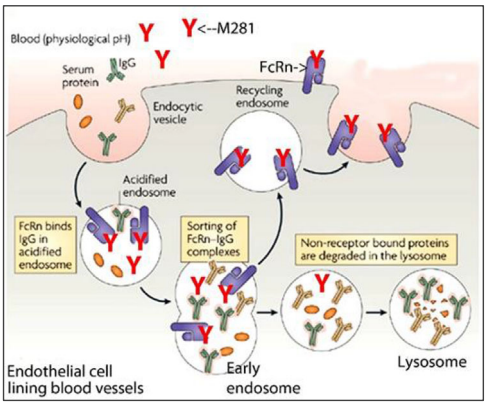
Fig 1. M281, a fully human, effectorless IgG1 monoclonal antibody binds competitively and with high affinity at ph 6·0 or ph 7·4 to the IgG binding site of FcRn, a transmembrane endososomal receptor for IgG and albumin. M281 has no effect on IgM, IgA, IgE, or cellular response to immunisation. (© Momenta Pharmaceuticals Inc. All rights reserved).

Blocking Maternal to fetal IgG transport across the placenta



Anticipated 1° mechanism for efficacy in pathogenic IgG-induced diseases of the fetus and newborn

Decreased Systemic IgG by blocking maternal FcRn-dependent IgG recycling



Seen in first-in-human study and expected in maternal circulation

Fig 2. Schematic diagram of FcRn function and M281 blockade (adapted from Roopenian and Akilesh,[21] © Momenta Pharmaceuticals Inc. All rights reserved).

related complication rate to 3·3% with a perinatal loss rate of 1·8%.[44] These data also support these invasive therapeutic procedures being performed in a centre with high numbers of cases with experience and expertise. Therefore overall, the success of intrauterine intravascular blood transfusion is well established with high survival and low complication rates. Furthermore, long-term outcome in surviving children is excellent, especially if fetal therapy is started before the onset of hydrops.[47]

However, if it is necessary to perform intrauterine intravascular transfusion before 22 weeks, the small anatomical dimensions of the fetal vasculature make the procedure associated with higher overall fetal mortality and procedure-related complication rates. Two small retrospective case cohort series have demonstratd the risks of early intrauterine transfusions.[32,48] A series of thirty intrauterine transfusions performed before 22 weeks (range 16–22 weeks) in Toronto (with access via heterogeneous vascular sites) noted a procedure-related complication rate of 6·7% and an overall perinatal loss rate of 20%.[32] A case series of 29 intrauterine transfusions performed prior to 20 weeks (range 16–19+6 weeks) from Leiden University Medical Center in The Netherlands[48] demonstrated a procedure-related complication rate of 5% and a non-procedure-related complication risk of 11% (per procedure). The perinatal loss rate overall (per fetus) was 24%, with 85% of losses occurring before 20 weeks. Intrauterine transfusion in obese women (BMI ≥ 30) prior to 20 weeks of gestation can be performed by ultrasound-guided intracardiac puncture with comparable outcomes when stratified for gestation.[49] Others have attempted to identify fetal anaemia early and perform fetal intraperitoneal transfusion prior to 20 weeks, temporarily prolonging gestation when the intrauterine fetal intravascular transfusion will be performed.[50] It is these high-risk pregnancies with early-onset fetal anaemia (prior to 22 weeks) and with high rates of procedure-related fetal loss, which would most benefit from medical treatments to ameliorate the alloimmune antibody effects of RBC destruction in HDFN. It was for this reason that the UNITY study had the inclusion criteria of previous pregnancies being severely anaemic prior to 24 completed weeks as a subsequent pregnancy will on average be susceptible to fetal anaemia 4–6 weeks earlier (see below).

Fetal and neonatal morbidity and mortality

"Rhesus" alloimmunisation causes in excess of 50 000 stillbirths *per annum* worldwide.[51] In 2010, an estimated 373 300 neonates were affected by HDFN globally, although countries with almost universal antenatal care have reduced the prevalence to 2·5/100 000 live births.[51] Prematurity (mostly iatrogenic) and the presence of hydrops fetalis (at delivery) worsens the overall outcome of these pregnancies.

Neonatal jaundice is treated with phototherapy or exchange transfusion[52] and IVIg appears limited in its role for the neonatal management of HDFN.[53] Cholestatic

jaundice (in 13% of neonates with HDFN) is independently associated with IUT.[54] Maternal antibodies may persist in the neonatal circulation for up to six months, leading to ongoing RBC destruction. Multiple neonatal top-up transfusions may be required.[52] Long-term outcomes after HDFN have been described in a recent review.[55]

Maternal therapy

Potential medical therapies for alloimmunised pregnancies must either act to: (i) reduce the amount of circulating maternal IgG antibody (by preventing its production); (ii) enhance its elimination from the maternal and fetal circulations; (iii) prevent IgG anti-RBC antibody 'transplacental transport' (due to FcRn) into the fetal circulation; iv) or alter the interaction between the antibody and target fetal antigen. Maternal (or fetal) immunosuppression can have life-threatening side effects and a principle of fetal therapy is to minimise complications to the mother.[56,57] In addition, such maternal therapies may be expensive, time-consuming and demanding on healthcare resources.

The immune system has a memory so alloimmunised women will mount a more efficient immune response to repeat exposure to the same RBC antigen in a future pregnancy, with HDFN expected to occur earlier and with increased severity.[45] Arguably the greatest need is to discover an effective treatment for the group of high-risk pregnancies where the early-onset disease makes them liable to undergo multiple invasive treatments with the associated perinatal hazards.

Maternal immunomodulation therapy

Azathioprine, promethazine and prednisolone have been proposed as immunomodulatory therapies to prevent red cell alloimmunisation[58] but evidence is limited to small cohort case series and such therapies are rarely used.[59] Mouse models of 'peptide immune therapy' to alter the recognition of the red cell antigens by T-helper cells to induce active tolerance have yielded promising results but there have been no subsequent reports of this potential therapy.[60]

Plasma exchange

Maternal plasma exchange has historically been used to clear alloantibodies from the maternal circulation but it is non-selective. This leads to loss of electrolytes and important proteins like coagulation factors and other immunoglobulins. Plasmapheresis can be used in high-risk women with previous severe HDFN.[61] Other concerns with this technique relate to altered maternal haemodynamics and reduced placental perfusion as well as the impact on resources as it requires specialist skills for vascular access and delivery. A rebound increase in antibody levels after therapeutic plasma exchange occurs due to immune activation as autoregulatory factors are removed.[62,63] Combining serial plasmapheresis with IVIg infusion has been shown to reduce this problem[64] and personalisation of treatment in cases of severe alloimmunisation using treatment with immunoadsorption and intravenous IVIg has been used with good outcomes.[65] This technique is rarely now practiced in the management of severe maternal red cell alloimmunisation, certainly not often in the UK.

Intravenous immunoglobulin (IVIg)

High-dose immunoglobulins were first used as a treatment for autoimmune disease in 1981 when they were shown to reduce platelet clearance in a child with immune thrombocytopenia.[66] This therapeutic strategy is somewhat paradoxical, as the original therapeutic use of IVIg was as an antitoxin to treat infectious disease (before antibiotics were available) and in immunodeficiency as replacement therapy.[67]

The use of maternal IVIg may postpone or even replace invasive intrauterine transfusions in fetuses in mothers with severe alloimmunisation in previous pregnancies.[50,68] IVIg works by diluting maternal alloantibodies, inducing competitive inhibition to block the transport of IgG across the placenta, increasing antibody 'turnover', blocking fetal secondary macrophage function and by reducing the pregnant patient's own antibody production.[69,70] IVIg will not be beneficial once HDFN has progressed to clinically significant fetal anaemia, but initial data from case series showed a survival benefit by delaying the natural history of the condition and 'buying time' to achieve a more advanced gestation.[50,71–73] However, IVIg is a derived blood product that had the theoretical risk for infectious complications. IVIg can cause systemic adverse reactions, such as fever, urticarial (type I hypersensitivity) reaction, haemolytic anaemia, aseptic meningitis, thrombosis and especially maternal headaches which can occur in up to 15% of those receiving infusions.[74] In addition, it is relatively expensive ($6 000/£4 800/€5 500 per week) therefore posing significant health economic challenges.[75]

The 'Postponing Early intrauterine Transfusion with Intravenous immunoglobulin Treatment' (PETIT) study was an international collaboration, pooling multicentre, retrospective observational cohort study data. Cases were enrolled with a qualifying pregnancy which was affected by HDFN prior to 24 weeks and a subsequent alloimmunised pregnancy would be affected by an antigen-positive fetus treated with or without IVIg.[76] The 'treatment group' comprised 24 women who received IVIg (at a dose of 1 g/kg maternal weight per week). There was a 'control' group of 28 women who were not treated with IVIg, and each of the 52 women also served as their own control as outcomes in each pregnancy were compared. Overall IVIg therapy appeared to delay the onset of clinically significant anaemia compared to the previous pregnancy by 15 days as compared to the group not treated with IVIg where the delay was nine days. IVIg also appeared to reduce

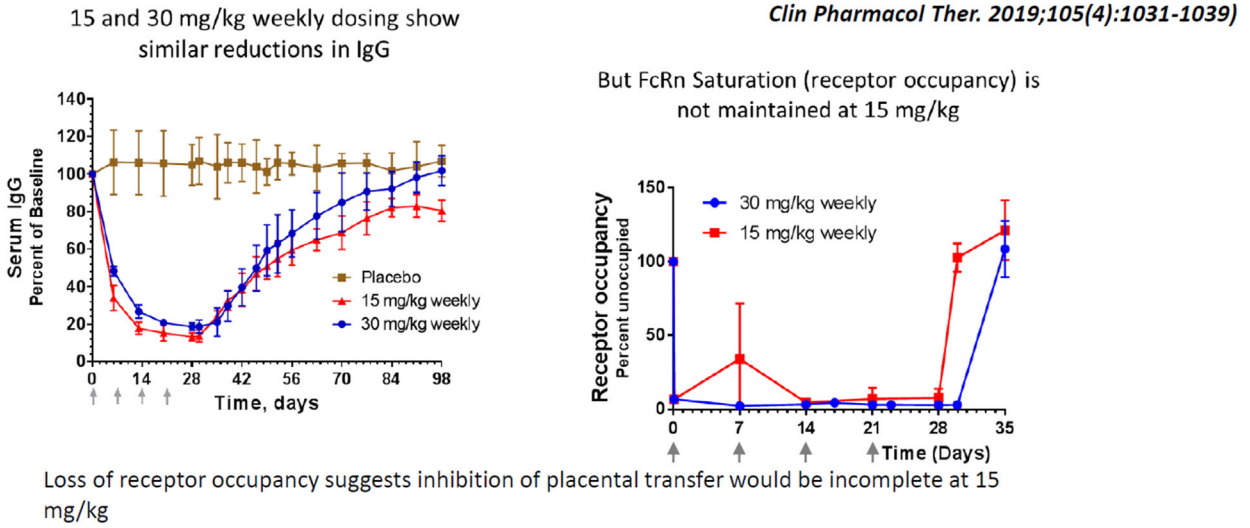


Fig 3. Adult healthy, non-pregnant volunteers (28 men and 22 women) received multiple doses (15 and 30 mg/kg) or placebo weekly for four weeks. IgG levels were followed for 14 weeks in total and FcRn receptor occupancy was determined up to five weeks after the first dose. While IgG reductions were similar for both M281 doses studied, only the 30 mg/kg dose maintained full FcRn receptor occupancy (adapted from Ling et al.[77]). [Colour figure can be viewed at wileyonlinelibrary.com]

the overall incidence of fetal hydrops [4% vs. 24%, odds ratio (OR) 0·03; 95% confidence interval, 0–0·5; $P = 0·011$] and the need for neonatal exchange transfusion (9% vs. 37%; OR: 0·1; 95% confidence interval, 00·5; $P = 0·009$). Overall survival was 88%, with no difference between groups (IVIg or control groups).[76] A subgroup analysis indicated that if the IVIg was initiated before 13 weeks of gestation, fetal anaemia was delayed by 25 days as compared to the previous pregnancy. Anaemia prior to 20 weeks gestation occurred less often (23%) as compared to the untreated previous pregnancy (54%).

Experimental monoclonal antibody therapy: M281 (nipocalimab) — the rationale for the clinical UNITY study (NCT03755128)

Recently, M281, a next-generation Fc receptor (FcRn) blocking agent has emerged which aims to address the continued unmet need for an effective non-surgical intervention for pregnant mothers with HDFN, especially for those likely to require IUT during early gestation when the procedure-related risks are relatively high.[77,78] M281, also known as *nipocalimab*, is a fully human, recombinant, aglycosylated IgG1 monoclonal antibody formulated for intravenous infusion. M281 binds with high affinity and specificity to the IgG binding site of FcRn. Since FcRn mediates the transfer of IgG from mother to fetus, M 281 has the potential to inhibit IgG transport across the placenta including the transfer of anti-red cell alloantibodies (Fig2). FcRn also acts to salvage IgG from degradation during normal internalization of circulating proteins into endothelial cells.[21] This process of IgG recycling maintains the long half-life of IgG and thus the blockade of FcRn–IgG binding is expected to decrease IgG half-life and serum concentrations including those of pathogenic IgG.[79,80] These mechanisms have also been postulated for IVIg where high concentrations of administered IgG can compete with endogenous IgG for placental transport and recycling as discussed above. M281 has greater than 1 000-fold higher affinity binding to FcRn than IgG and thus may be much more efficient in inhibiting these processes.

In preclinical studies, M281 demonstrated inhibition of placental IgG transfer from maternal to fetal circulation in the human placental perfusion model within 4–6 h, suggesting rapid saturation of FcRn and a fast onset of action .[81] Insignificant transfer of M281 from maternal to fetal circulation was noted suggesting a lower risk of fetal and neonatal drug exposure with maternal M281 administration (Table I). In addition, an analogous murine anti-FcRn antibody has been reported to protect murine fetuses from thrombocytopenia due to maternal antiplatelet antibodies[82] and from miscarriage due to maternal antibodies inducing placental damage.[83]

M281 was well tolerated in the first-in-human study with no serious or severe adverse events and primarily mild adverse events with similar frequency as placebo.[77] As predicted by its mechanism of action and preclinical studies, M281 induced rapid dose-dependent lowering of serum IgG upon administration of single and multiple doses (Fig 3). In addition, M281 was observed to lower serum albumin albeit to a lesser extent than for IgG, an effect that may be related to FcRn's role in albumin homeostasis.[79] These albumin decreases seen with M281 in human volunteers were modest and asymptomatic. Similarly, no significant adverse effects

Table I. M281 inhibition of IgG transfer from maternal to fetal circulation.

Maternal circuit M281 (μg/ml*)	Maternal circuit adalimumab (μg/ml*)	Fetal circuit adalimumab at study end, mean (*SD*) (μg/ml)	Fetal transfer rate Adalimumab, mean (*SD*) (%)	*P* value†	Number of studies	Experimental period (h)
0	270	0·50 (0·5)	0·23 (0·21)	NA	8	6
10	270	0·12 (0·02)	0·07 (0·01)	<0·001	3	6
300	270	0·12 (0·01)	0·06 (0·01)	<0·001	5	6

Ex-vivo, dual perfusion human placental cotyledon experiments demonstrating M281 monoclonal antibody inhibits IgG transfer with minimal M281 transfer to the fetal circulation (adapted from Roy et al.[81]).

Mean antipyrine fetal transfer rate for these studies was 41·7 ± 2·7% for adalimumab alone and 43·8 ± 4·2% for all adalimumab plus M281 studies. Fetal transfer rate = 100× concentration of the test substance in the fetal circuit at the end of the experimental period/concentration of the test substance in the maternal circuit at the start of the experimental period.

*Concentration of test compounds in the maternal perfusate at initiation of the experimental period.

†P values were calculated compared with no M281 using a linear mixed-effects model with random slope and intercept.

have been noted in studies of other anti-FcRn agents in autoimmune patients.[79] In addition, early concerns regarding increased risk of infection related to the inhibition of FcRn-mediated lowering of IgG serum concentrations have not been confirmed by preliminary data with M281 or other anti-FcRn agents.[79] Antagonists of FcRn do not affect other antibody classes and in particular the IgM response to new antigen is preserved so it is possible that the ability to fight infection could be preserved.[84] These findings confirming the mechanism of action and tolerability of M281 and that of similar agents support the evaluation of FcRn antagonism in an indication such as HDFN where transfer pathogenic antibodies result in severe disease and poor outcomes.

Thus in 2019, UNITY (NCT03755128), a multicentre, open-label, proof of principle (phase II) clinical study, was initiated by clinical chief investigators, Dr Kenneth J. Moise (University of Texas, Houston, TX, USA) and Dr Dick Oepkes (Leiden University Medical Center, Leiden, The Netherlands), and sponsored by Momenta Pharmaceuticals Inc. (Cambridge, MA, USA) (Clinical Trial Gov. https://clinicaltrials.gov/ct2/show/NCT03842189?term=M281&draw=2&rank=2).

UNITY is designed to evaluate the potential of weekly intravenous M281 to delay or prevent the need for IUT in pregnant mothers at risk of early-onset HDFN prior to 24 weeks, the same population analysed in the PETIT study. M281 is initiated upon confirmation of positive fetal antigen status at approximately 14 weeks gestation. Weekly dosing until 35 weeks aims to block placental IgG transfer of pathogenic alloantibodies for as long as possible. The study will enrol 15 pregnant women affected by early-onset HDFN. Primary end-points in the study are maternal and infant safety and efficacy as determined by the frequency of live births at ≥32 weeks gestational age without the requirement for an IUT throughout pregnancy. Given the rarity of this patient cohort, collaboration between international centres will be required to attain adequate enrolment and obtain the highest level of evidence, whilst ensuring maternal and fetal well-being and safety during the experimental phase. Robust safety of data for this experimental therapy, including detailed pharmacodynamic and pharmacokinetic data in pathologic pregnancies, as well as short and long-term follow-up of surviving children is mandatory.

Conclusion

Haemolytic disease of the fetus and newborn is an alloimmune pathology associated with an increased risk of perinatal mortality and neonatal morbidity, both from prematurity and the direct effects of anaemia and hyperbilirubinaemia. A small but significant cohort of women with red cell alloimmunisation are at risk of developing early-onset fetal anaemia and although IUT is possible (prior to 22 weeks), it carries increased risk of procedure-related complications including miscarriage. In these patients, IVIg administered late in the first trimester may postpone the gestational age when an IUT is required to a technically safer time. A novel strategy to inhibit transplacental alloantibody transfer with maternal M281 monoclonal antibody therapy is under evaluation with potential for greatest impact in these alloimmunised pregnancies at risk of early-onset fetal anaemia.

Funding information

No external funding required.

Author contributions

JSC and MDK researched and wrote the article. MDK and KJM instigated, reviewed and edited the article. All authors approved the final version.

Conflicts of interest

Professor Moise and Professor Kilby receive no direct funding from Momenta Pharmaceuticals. The McGovern School of Medicine, Houston and Birmingham Women's and

Children's Research & Development/University of Birmingham, UK receives funding from Momenta for the ongoing phase II clinical trial.

Data availability statement

There are no original data presented in this review article. Data from published studies are referenced.

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